PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P211551PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NL2004/000750	International filing date *(day/month/year)* 25.10.2004	Priority date *(day/month/year)* 24.10.2003
International Patent Classification (IPC) or national classification and IPC A61K31/70, A61K31/732, A61P37/00		
Applicant N.V. NUTRICIA		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 24.08.2005	Date of completion of this report 24.02.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Paul Soto, R Telephone No. +49 89 2399-7346

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NL2004/000750

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-28 as originally filed

Claims, Numbers

1-15 received on 30.01.2006 with letter of 30.01.2006

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NL2004/000750

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3, 4, 11-15
	No:	Claims	1, 2, 5-10
Inventive step (IS)	Yes:	Claims	4
	No:	Claims	1-3, 5-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

PCT/NL2004/000750

1. Reference is made to the following documents:

D1: DATABASE WPI Section Ch, Week 198307 Derwent Publications Ltd., London, GB; Class A96, AN 1983-16545K XP002277416 & JP 58 004724 A (MEIJI MILK PROD CO LTD) 11 January 1983;

D2: DATABASE WPI Section Ch, Week 200332 Derwent Publications Ltd., London, GB; Class B03, AN 2003-339110 XP002277417 & KR 2002 094 725 A (KT & G CO LTD) 18 December 2002;

D3: DATABASE WPI Section Ch, Week 199249 Derwent Publications Ltd., London, GB; Class A96, AN 1992-403412 XP002277418 & JP 04 300888 A (DAINIPPON INK & CHEM KK) 23 October 1992;

D4: DATABASE WPI Section Ch, Week 199441 Derwent Publications Ltd., London, GB; Class B04, AN 1994-329946 XP002277419 & JP 06 256208 A (FOOD DESIGN GIJUTSU KENKYU KUMIAI) 13 September 1994;

D5: DATABASE WPI Section Ch, Week 199624 Derwent Publications Ltd., London, GB; Class B04, AN 1996-236112 XP002277420 & JP 08 092303 A (SHOWA SANGYO CO) 9 April 1996;

D6: ZAPOROZHETS T S ET AL: "[Immunomodulating properties of pectin from seawater grass Zostera]" ANTIBIOTIKI I KHIMIOTERAPIIA = ANTIBIOTICS AND CHEMOTERAPY [SIC] / MINISTERSTVO MEDITSINSKOI I MIKROBIOLOGICHESKOI PROMYSHLENNOSTI SSSR. USSR AUG 1991, vol. 36, no. 8, August 1991 (1991-08), pages 31-34, XP009028863

D7: FR-A-2 781 673 (UNIV PICARDIE) 4 February 2000;

D8: PATENT ABSTRACTS OF JAPAN vol. 012, no. 159 (C-495), 14 May 1988 (1988-05-14) & JP 62 270532 A (NODA SHIYOKUKIN KOGYO KK;OTHERS: 01), 24 November 1987;

D9: KULKARNI SAVITA ET AL: "Immunostimulant activity of inulin isolated from Saussurea lappa roots." INDIAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 63, no. 4, July 2001, pages 292-294, XP009029650

D10: DATABASE EPODOC EUROPEAN PATENT OFFICE, THE HAGUE, NL; XP002277425

D11: US-A-4 412 946 (SALLES MARIE-FRANCE ET AL) 1 November 1983;

D12: WO 01/33975 A (BIJLSMA PIETER BRANDT ;GROOT JACQUES

ALPHONS (NL); TIMMERMANS JOHA) 17 May 2001;

D13: WO 00/57727 A (BIJLSMA PIETER BRANDT ;GROOT JACQUES ALPHONS (NL); TIMMERMANS JOHA) 5 October 2000;

D14: WO 02/47703 A (HAGEMAN ROBERT JOHAN JOSEPH ;NUTRICIA N V (NL); GRAUS YVO MARIA FR) 20 June 2002;

D15: US-B1-6 573 245 (MARCIANI DANTE J) 3 June 2003;

D16: US 2003/022863 A1 (STAHL BERND ET AL) 30 January 2003;

D17: WO 02/42484 A (SUEDZUCKER AKTIENGESELLSCHAFT MANNHEIM/OCHSENFURT; KUNZ, MARKWART; MUN) 30 May 2002;

D18: PATENT ABSTRACTS OF JAPAN vol. 1997, no. 12, 25 December 1997 (1997-12-25) & JP 09 208474 A (POLA CHEM IND INC), 12 August 1997;

D19: PATENT ABSTRACTS OF JAPAN vol. 1997, no. 06, 30 June 1997 (1997-06-30) & JP 09 048732 A (POLA CHEM IND INC), 18 February 1997;

D20: GB-A-1 327 740 (RECHERCHE ET INDUSTRIE THERAPEUTIQUES) 22 August 1973;

D21: EP-A-0 406 685 (HOECHST AKTIENGESELLSCHAFT) 9 January 1991

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. The present application relates to the use of acid oligosaccharide (AcOl) and neutral oligosaccharide (NeOl) in the manufacture of a composition for use in a method for the treatment and/or prevention of an immune system related disorder (**claim 1**), and for use in a method for enhancing the immune response in a mammal (**claim 2**), said method comprising administering to said mammal a composition comprising a therapeutically effective amount of AcOl and NeOl, wherein:
-the AcOl has a degree of polymerisation (DP) between 1 and 250 and is prepared from pectin or alginate; and
-the NeOl is selected from the group consisting of fructans, fructooligosaccharides, indigestible dextrins, galactooligosaccharides (including transgalactooligosaccharides), xylooligosaccharides, arabinooligosaccharides, glucooligosaccharides, mannooligosaccharides, fucooligosaccharides and mixtures thereof.

Claim 12 is directed to a food composition comprising 5-50 % lipid, 10-60 % protein, 15-90% carbohydrate, AcOl and NeOl, wherein said AcOl comprises at least one terminal uronic acid unit, has a DP between 1 and 250 and is prepared from pectin or alginate; and said NeOl is selected from the group as specified in claims 1 and 2. Finally, **claim 15** relates to a liquid composition comprising fat, carbohydrate and protein, and comprising per 100 ml of the liquid composition, 0.5-1 g soluble indigestible oligosaccharides, 0.4-0.7 g indigestible $[galactose]_n$-glucose comprising beta-linked saccharides; wherein n is an integer between 1 and 60, i.e. 2, 3, 4, 5, 6,... 59, 60; and 0.01-0.1 g indigestible polysaccharide carbohydrate comprising a chain of at least 10 beta-linked fructose units; and 0.04-0.3 g AcOl which have a degree of polymerisation between 1 and 250 and are prepared from pectin or alginate.

3.1. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2)). **D16** (see also paragraphs 23, 25, 31, 32, 37, 39 and examples 8 through 13) discloses preparations of an antiadhesive carbohydrate, which is an acid oligosaccharide, which serves for reducing and/or blocking the adhesion of pathogenic substances and organisms to eucaryotic cells. The adhesion of pathogenic organisms to the surface of mammal cells is the first step and an indispensable prerequisite for an infection or a damage of the cell (see paragraph 2 in **D16**). Thus, the therapeutic purpose addressed in **D16** is considered to overlap with those claimed in the present application, namely "the treatment and/or prevention of an immune system related disorder in a mammal" (**claim 1**) and "for enhancing the immune system in a mammal" (**claim 2**). Furthermore, the DP of the antiadhesive carbohydrate fall within the interval claimed in the present application and is prepared from pectin or alginate (see also examples 1-7 in **D16**). The preparations may also contain besides the antiadhesive carbohydrates also a prebiotic carbohydrate which falls within the definition of neutral oligosaccharide of the present claims. Furthermore, in example 8 of **D16** the prebiotic carbohydrate mixture consists of galactooligosaccharides and inulin (Raftiline) in a ratio of 9:1 which is the same mixture of neutral oligosaccharides as that preferred in the present application (see last paragraph on page 23 and the examples of the application). Thus, **D16** is found novelty destroying for present claims 1, 2 and 5-10.

3.2. The subject-matter of present claims 3, 4, and 11-15 is novel over the prior art.

4.1. However, no inventive step is recognised for the subject-matter of present claims 3 and 11-15 for the following reasons. **D16** is regarded by this International Preliminary Examining Authority as the closest prior art.

(a) The subject-matter of present **claim 11** differs from **D16** in that the composition is adapted for administration to a human specifically in the age of 0-1 year.

Thus, the problem to be solved by the present application according to said claim is regarded in the selection of a particular group of patients for which the composition is suitable. The solution provided in the present application according to claim 11 is obvious. **D16** (see paragraph 31 and claim 13) discloses that the preparation disclosed therein may be incorporated in any desired food, which indeed includes baby food. The selection of this specific group of patients (babies of 0-1 year) does also not appear to relate to any technical effect which is not present in other groups of patients (older than 1 year). Accordingly, this can not be regarded as an inventive selection.

(b) The subject-matter of present **claim 12** differs from **D16** in that a specific range of lipids, protein and carbohydrate is specified for the food composition. Present **claim 15** differs from **D16** in that specific amounts of soluble indigestible oligosaccharides (neutral oligosaccharides) and acid oligosaccharides are specified as well as in the fact that the food composition is liquid. No inventive step is acknowledged in either these technical features or those of present claims 13 and 14 since they merely consist in the selection of particularly preferred embodiments which are determined empirically, without the exercise of inventive skill, or fall anyway within the customary practise followed by those skilled in the art.

© The subject-matter of present **claim 3** differs from **D16** in that the immune system related disorders treated are selected from the group consisting of an autoimmune disorder, hereditary or conditional induced immunodeficiency, support for vaccinations, allergy Type 1, allergy Type 2, allergy Type 3 and allergy Type 4.

The specific treatment and/or prevention of autoimmune disorders, hereditary or conditional induced immunodeficiencies or support for vaccination according to present claim 3 could only involve an inventive step if it was shown that the combination of AcOl

and NeOl according to the claims related to any advantage or surpring effect *in connection with the treatment of said diseases*. However, the application does not contain any technical data showing that the specific mixture of AcOl and NeOl according to claim 3 provides an advantageous or surprising effect in connection with the treatment and/or prevention of autoimmune disorders, hereditary or conditional induced immunodeficiencies or support for vaccination. Consequently, no inventive step can be recognised.

4.2. However, in which concerns the treatment and/or prevention of allergy Type 1, allergy Type 2, allergy Type 3 and allergy Type 4 according to present **claim 4** the application shows a synergistic effect in the reduction of Th2 response (see paragraph linking pages 1 and 2, and Table 3 on page 27 of the application) for the specific combination of acid and neutral oligosaccharides. The use of neutral oligosaccharides and acid oligosaccharides in the treatment and/or prevention of allergy is known from **D12** and **D13** (see lines 2-12 on page 4), respectively. However, a synergistic effect for the combination could have not been predicted from the prior art. Accordingly, an inventive step is recognised for the subject-matter of present claim 4.

5.1. **Claims 12-15** meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

5.2. For the assessment of the present **claims 1-11** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment, as it is the case of present claims 1-11.

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IAP12 Rec'd PCT/PTO 24 APR 2006

AMENDED CLAIMS WITH LETTER OF 30 JANUARY 2006

1. Use of acid oligosaccharide and neutral oligosaccharide in the manufacture of a composition for use in a method for the treatment and/or prevention of an immune system related disorder in a mammal, said method comprising administering to said mammal a composition comprising a therapeutically effective amount of acid oligosaccharide and neutral oligosaccharide, wherein:

- the acid oligosaccharide has a degree of polymerization between 1 and 250 and are prepared from pectin or alginate; and
- the neutral oligosaccharides wherein the neutral oligosaccharide is selected from the group consisting of fructans, fructooligosaccharides, indigestible dextrins, galactooligosaccharides (including transgalactooligosaccharides), xylooligosaccharides, arabinooligosaccharides, glucooligosaccharides, mannooligosaccharides, fucooligosaccharides and mixtures thereof.

2. Use of acid oligosaccharide and neutral oligosaccharide in the manufacture of a composition for use in a method for enhancing the immune response in a mammal and/or a method for modulating the immune system in a mammal, said method comprising administering to the mammal a composition comprising acid oligosaccharide and neutral oligosaccharide, wherein:

- the acid oligosaccharide has a degree of polymerization between 1 and 250 and are prepared from pectin or alginate; and
- the neutral oligosaccharides wherein the neutral oligosaccharide is selected from the group consisting of fructans, fructooligosaccharides, indigestible dextrins, galactooligosaccharides (including transgalactooligosaccharides), xylooligosaccharides, arabinooligosaccharides, glucooligosaccharides, mannooligosaccharides, fucooligosaccharides and mixtures thereof.

3. Use according to claim 1, wherein the immune system related disorder is selected from the group consisting of autoimmune disorders, hereditary or conditional induced immunodeficiency, support for vaccinations, allergy Type 1, allergy Type 2, allergy Type 3 and allergy Type 4.

4. Use according to claim 1, wherein the immune system related disorder is selected from the group consisting of allergy Type 1, allergy Type 2, allergy Type 3 and allergy Type 4.

5. Use according to any one of the preceding claims, wherein the acid oligosaccharide comprises at least one terminal uronic acid unit.

6. Use according to claim 5, wherein the uronic acid unit is selected from the group consisting of galacturonic acid, glucuronic acid, guluronic acid, iduronic acid, mannuronic acid, riburonic acid and alturonic acid.

7. Use according to claim 1, wherein the neutral oligosaccharide selected is from the group consisting of galactooligosaccharide, fructooligosaccharide and transgalactooligosaccharide.

8. Use according to any one of the preceding claims, wherein the composition comprises two chemically distinct neutral oligosaccharides, one selected from the group consisting of galactose based neutral oligosaccharide and one selected from the group of fructose and/or glucose based oligosaccharide.

9. Use according to claim 8, wherein the composition comprises fructooligosaccharide and at least one selected from transgalactooligosaccharride and galactooligosaccharide.

10. Use according to any one of the preceding claims, wherein the method comprises the enteral administration of the composition.

11. Use according to any of the preceding claims, wherein the composition is administered to a human in the age of 0-1 year.

12. A food composition comprising between 5 and 50 en% lipid, between 10 and 60 en% protein, between 15 and 90 en% carbohydrate, acid oligosaccharide and neutral oligosaccharide, wherein said acid oligosaccharide comprises at least one terminal uronic acid unit, has a degree of polymerization between 1 and 250 and are prepared

from pectin or alginate; and said neutral oligosaccharide is selected from the group consisting of fructans, fructooligosaccharides, indigestible dextrins, galactooligosaccharides (including transgalactooligosaccharides), xylooligosaccharides, arabinooligosaccharides, glucooligosaccharides, mannooligosaccharides, fucooligosaccharides and mixtures thereof.

13. Composition according to claim 12, wherein the composition has a caloric density between 0.1 and 2.5 kcal/ml.

14. Composition according to any of claims 12 or 13, wherein the composition has a viscosity below 250 mPas at a shear rate of 100 s^{-1} at 20°C.

15. Liquid composition comprising fat, carbohydrate and protein and comprising, per 100 ml of the liquid composition, between 0.5 and 1 g soluble indigestible oligosaccharides, comprising between 0.4 and 0.7 g indigestible $[galactose]_n$-glucose comprising β-linked saccharides; wherein n is an integer between 1 and 60, i.e. 2, 3, 4, 5, 6, ..., 59 ,60; between 0.01 and 0.1 g indigestible polysaccharide carbohydrate comprising a chain of at least 10 β-linked fructose units; and between 0.04 and 0.3 g acid oligosaccharides has a degree of polymerization between 1 and 250 and are prepared from pectin or alginate.